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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,879	06/22/2000	MICHAEL GIESING	790076.401	6896

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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 10/04/2002

20

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/485,879

Applicant(s)

GIESING ET AL.

Examiner

Jeanine A Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 21,22,24-39 and 41-59 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21,22,24-39 and 41-59 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

### **DETAILED ACTION**

1. This action is in response to the papers filed June 28, 2002. Currently, claims 21-22, 24-39, 41-59 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
2. Any objections and rejections not reiterated below are hereby withdrawn. The action contains new grounds of rejection necessitated by amendment, therefore, the arguments directed to the old ground of rejections are moot.

### ***Priority***

3. This application is a 371 of PCT/EP/98/05360, filed August 24, 1998. This application also claims priority to foreign document 197 36 691.0, filed August 22, 1997, however, a translation of this document has not been provided.

Applicant's request clarification from the Examiner regarding the reference to the priority document in the first paragraph. The examiner has not required or even requested a translation. The examiner has merely indicated that the translation has not been provided.

### **New Grounds of Rejection Necessitated by Amendment**

### ***Election/Restrictions***

4. Claims 38-39 have been rejoined with the pending claims and have been examined on their merits.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jung et al. (Eur. J. Clinical Chemistry and Clinical Biochemistry. Vol. 35, No. 1, pages 3-10 January 1, 1997) and Rimm et al (US Pat. 6,197,523, March 2001) or Ts'o et al (US Pat 5,962,237, October 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000).

This rejection is based upon the interpretation of the claims to encompass detection of a nucleic acid in both an enriched sample and in a sample which has not been enriched for cancer cells.

Jung et al. (herein referred to as Jung) teaches the quality management and influential factors for the detection of single metastatic cancer cells by reverse transcriptase polymerase chain reaction. Jung teaches that the amplification of tissue-specific gene expression, by RT-PCR readily detects single tumor cell sin different tissues. Jung teaches the method is sensitive and specific for detection of mircrometataasis which holds great promise for earlier staging of cancer patients (abstract). Jung provides a table of genes which have been detected using RT-PCR. Jung teaches numerous reasons why it is advantageous to perform a high-sensitivity RT-PCR on peripheral blood sample, including ease for patient, ease for lab in assaying and sensitivity and specificity (page 5, col. 1)(limitations of Claim 41b)

Rimm et al (herein referred to as Rimm) teaches a method for the detection, identification, enumeration and confirmation of circulating cancer and or hematologic progenitor cells in whole blood. Rim teaches the analysis involved epitopic examination of the blood sample, while the blood sample is disposed in a centrifuged blood sampling tube such that the epitopic analysis of the presence or absence of cancer cells relies on the detection of epitopes which are known to be present only on cancer cells (abstract). Rimm teaches that epithelial-specific antigens such as CEA may be used (limitations of Claim 23-26)(col. 4, lines . 49-52). Rimm teaches that "additional scans depending on what additional cellular information is being sought" may be used (col. 9, lines 53-60). The analysis of additional cancer cell-specific epitopes which will enable the cytopathologist to identify the origin of the cancer cells would be useful. Rimm teaches that "since the analysis of this invention is non-destructive of the cells, the cells may be

removed from the sampling tube for additional analysis by other methods such as PCR (col. 12, lines 8-11)(limitations of Claim 41c).

Ts'o et al (herein referred to as Ts'o) teaches obtaining a sample comprising cancer cells and non-rare cells, subjecting the sample to multiple density gradient separation, subjecting the second fluid to a binding agent that binds non-rare cells and removes the bound non-rare cells from the fluid such that the fluid is enriched with a greater density of cancer cells (abstract). Ts'o teaches further processing the rare cells to detect expression of specific nucleic acids, chromosomal changes. FISH and combination staining are taught to provide improved methods of diagnosis, staging, and monitoring cancer in a patient (col. 2, lines 45-58). In a specific example, Ts'o teaches that in the case of separation of cancer cells from blood, it was found that cancer cells could be almost completely separated from nucleated white blood cells to provide the benefit of removing nucleated white blood cells which can interfere with cell identification, particularly wherein PCR methods are used (col. 11, lines 55-63). Ts'o teaches that rare cells can be also identified and or characterized using nucleic acid hybridization protocols.

Moreover, Hoon et al. (herein referred to as Hoon) teaches methods of using multiple cancer makers provide increased sensitivity over methods using single cancer markers. Hoon teaches the prior art was limited by their ability to discriminate cancer cells from normal cells also carrying the marker, thus reducing the specificity and reliability. Hoon teaches that "tumor, heterogeneity has caused sensitivity problems where a single-specific marker has been employed" (col. 2, lines 23-29). Hoon provides

a list of makers which are preferably detected, including tyrosinase, MAGE3, Cytokeratin 20 (col. 3, lines 15-30). Hoon teaches that the method is conducted at least twice on a given sample using at least two different primer pairs specific for two different specific markers (col. 4, lines 37-40). In a specific example, 15ml of blood was obtained from patients and collected in 5 sodium citrate tubes (col. 19, lines 22-23). The tubes were centrifuged and the buffy coat was removed. Analysis was performed on the blood specimens by PCR using multiple markers. The use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity of detecting melanoma cells that express few or no copies of tyrosinase mRNA (col. 21, lines 60-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have combined the methods of Dittkoff and Rimm because Hoon teaches that detection of multiple cancer makers provide increased sensitivity over methods using single cancer markers. Therefore, the ordinary artisan would have been motivated to have combined several cancer detection methods for several markers to increase sensitivity. The methods of Dittkoff and Rimm both are directed to methods which allow detection of cancer-associated or cancer-specific markers within a body fluid, namely blood, which indicates an increased risk for or the presence of a disseminated cancer cell. The method of Dittkoff detects amplification without the need for enrichment, whereas the method of Rimm isolates cancer cells and subsequently suggests performing additional analysis including PCR. The collection of two tubes of blood from a cancer patient or a patient suspected of having cancer and performing the analysis of

both Ditkoff and Rimm allows for the detection of multiple markers which increases sensitivity and increases the likelihood of early detection of cancer, as taught by Hoon. Jung teaches numerous reasons why it is advantageous to use peripheral blood including that it is less stressful for the patient and therefore may be performed on a routine basis together with other laboratory tests. Therefore, when blood is drawn from a patient having cancer or suspected of having metastasis, several tubes may be collected with minimal discomfort or stress for the patient. The multiple tubes of blood may be used for a variety of laboratory tests including RT-PCR and cancer cell isolation. As specifically provided by Hoon, detection of more than a single cancer marker is strongly recommended to provide more sensitive and accurate results. Therefore, analyzing a single patient's blood samples for more than one known cancer marker would have the expected benefit of minimizing the stress and pain inflicted on the patient while simultaneously obtaining sensitive and meaningful results to determine whether micrometastasis is present in the sample. The same cancer-specific or cancer associated marker may be detected in the enriched and unenriched sample in the event that no marker detection was seen in the unenriched sample, the ordinary artisan may be motivated to analyze an enriched sample in order to detect smaller quantities of the marker without background.

7. Claims 21-22, 27-37, 41-43, 45-49, 51, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmitz et al. (US Pat. 6,190,870, February 20, 2001) in view of Popescu et al (Cancer Genetics Cytogenet. Vol. 93, pg 10-21, 1997) or

Torczynski et al (US Pat. 5,589,579, December 1996) and in further view of Hoon et al (US Pat 6,057,105, May 2, 2000).

This rejection is based upon the broad interpretation of the claim which allows for both fractions to be enriched for cancer cells from non-cancer cells.

Schmitz et al (herein referred to as Schmitz) teaches that tumor cells, particularly carcinoma cells are separated from peripheral blood by magnetic sorting (abstract). Specifically Schmitz teaches that cell samples may be contacted with antibodies which are directed to tumor antigens or lineage specific antigens are used to magnetically label the tumor cells. The labeled cells are separated from unlabeled hematopoietic cells by magnetic separation. The fraction of cell enriched for tumor cells is useful for quantitating the tumor cells and as a source of tumor cells for further characterization (col. 3, lines 30-45). Schmitz provides a long list of separation markers which may be cell surface antigens or located in the cytoplasm of the tumor cells. These markers include EMA, HEA-125, C26, among many others (col. 4). Moreover, Schmitz teaches that tumor cells may be further characterized as to their phenotype by PCR, FISH in situ FISH competitive hybridization (col. 9, lines 4-6). Moreover, the expression of a number of proteins related to malignancy is of interest including oncogenes, erbB, myc, p53, drug resistance proteins, metastatic factors including metalloproteases, integrins, angiogenic factors and others (col. 9, lines 8-15)(limitations of Claims 33-36).

While Schmitz teaches that isolated tumor cells may be further characterized as to their phenotype by PCR or FISH, Schmitz fails explicitly exemplify identifying two cancer markers within separate fractions.

However, Popescu et al (herein referred to as Popescu) teaches that FISH is a powerful for detection of tumor cells. Popescu teaches that FISH is the most efficient and reproducible approach for precise localization of single sequences within metaphase chromosomes (pg 11, col. 2). Popescu also teaches that "FISH offers several approaches to identifying chromosomal translocations on the whole karyotype, by the use of combinatorial multiflour detection or spectral analysis and to characterizing specific translocations by hybridization with chromosome and single-copy gene probes and bi-and multicolor detection. For example, FISH with two chromosome probes permits the identification of complex rearrangements" (pg 15, col. 2).

Similarly, Torczynski et al (herein referred to as Torczynski) teaches FISH allows cells to be stained so that genetic aberrations resulting in changes in gene copy number of structure can be quantitated by fluorescent microscopy. The cell may be mounted on a microscope slide, in suspension or prepared from paraffin embedded material. FISH has been used to detect changes in gene copy number and gene structure; detection of genetic changes even in low frequency subpopulations and detection and measurement of the frequency of residual malignant cells (col. 3-4). Torczynski teaches that CEA has allowed the development of specific DNA probes which discriminate their expression in lung cancer at the mRNA level (col. 3, lines 25-30). Torczynski teaches that the ras family of oncogenes can be identified by differential hybridization of P-labeled mutated oligonucleotides. Moreover, the myc family of oncogenes are activated by overexpression of the cellular myc genes either by gene amplification or by rearrangements.

Hoon et al. (herein referred to as Hoon) teaches methods of using multiple cancer makers provide increased sensitivity over methods using single cancer markers. Hoon teaches the prior art was limited by their ability to discriminate cancer cells from normal cells also carrying the marker, thus reducing the specificity and reliability. Hoon teaches that "tumor, heterogeneity has caused sensitivity problems where a single-specific marker has been employed" (col. 2, lines 23-29). Hoon provides a list of makers which are preferably detected, including tyrosinase, MAGE3, Cytokeratin 20 (col. 3, lines 15-30). Hoon teaches that the method is conducted at least twice on a given sample using at least two different primer pairs specific for two different specific markers (col. 4, lines 37-40). In a specific example, 15ml of blood was obtained from patients and collected in 5 sodium citrate tubes (col. 19, lines 22-23). The tubes were centrifuged and the buffy coat was removed. Analysis was performed on the blood specimens by PCR using multiple markers. The use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity of detecting melanoma cells that express few or no copies of tyrosinase mRNA (col. 21, lines 60-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Schmitz to include the identification of the tumor cells with FISH, as taught by Popescu and Torczynski, rather than merely quantitating cancer cells as provided in Schmitz. Popescu and Torczynski both teach numerous benefits of FISH which include detection of translocations, changes in gene copy number and gene structure which would not be

readily apparent using quantitating mechanisms as provided by Schmitz. FISH is able to detect many mutations which are not morphologically evident. Therefore, in the event that both fractions are enriched for tumor cells, as provided by Schmitz, the ordinary artisan would be motivated to detect more than one cancer marker, as taught by Hoon, for the express benefit that detection of more than one cancer marker increases sensitivity. Thus, detection of two markers within the isolated tumor cells would have been ideal for increasing sensitivity and reliability in determining micrometastasis of cancer. Schmitz teaches numerous genes which are differentially expressed between cancer and normal cells, such that the ordinary artisan would be motivated to have selected any combination of such markers depending upon the suspected form of cancer in which they are studying or select a combination which is more general to cancers generically. With regard to Claims 41-43, the ordinary artisan would be motivated to have used the same first and second cancer-specific nucleic acids or different first and second nucleic acids. The ordinary artisan would have been motivated to have detected the same nucleic acids in both steps for the expected benefit of determining whether certain point mutations which were specific cancers was present or to detect certain point mutations which indicate the prognosis of the cancer.

8. Claims 38-39, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat. 5,976,797) in view of Jung et al. (Eur. J. Clinical Chemistry and Clinical Biochemistry. Vol. 35, No. 1, pages 3-10 January 1, 1997) and Rimm et al (US Pat. 6,197,523, March 2001) or Ts'o et al (US Pat 5,962,237, October 1999) in

view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 above.

Neither Schimitz, Popescu, Torczynski nor Hoon teach analyzing and identifying an anticancer therapy by administering an anticancer therapy to samples, and detecting the presence or expression of markers before and after to evaluate an anticancer therapy.

However, Mitsuhashi teaches a method for determining the cytotoxic effect of a compound by adding said compound to a sample, measuring mRNA present in sample and evaluating the cytotoxic effect of the compound. Mitsuhashi teaches studying vinblastine, cisplatin and mitomycin C.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Mitsuhashi for detecting cytotoxic effects of an anticancer compound such as cisplatin, for example, by detecting multiple markers in enriched and unenriched cultures. The ordinary artisan would have been motivated to have analyzed more than one mRNA for the reasons of specificity and reliability provided by Hoon. Determining the effect of an anticancer compound, or any compound, is accomplished by testing the nucleic acid expression prior to the administration of the compound, administering the compound and then comparing the expression following the compound administration. Therefore, the claimed methods are not novel with respect to the means in which an anticancer therapy is analyzed.

Art Unit: 1634

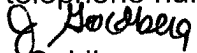
**Conclusion**


**9. No claims allowable over the art.**

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Jeanine Goldberg  
September 30, 2002

  
W. Gary Jones  
Supervisory Patent Examiner  
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